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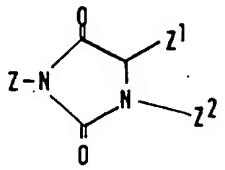
(54) HYDANTOIN ANALOGUES

(71) We, THE WELLCOME FOUNDATION LIMITED, of 183—193 Euston Road, London, N.W.1. a company incorporated in England do hereby declare that the invention for which we pray that a Patent may be granted to us and the method by which it is performed, to be particularly described in and by the following statement:—

This invention relates to heterocyclic compounds, their synthesis, compositions containing them, and their use in medicine.

Hydantoin derivatives, defined hereinbelow in formula (I), have been found to have pharmacological properties related to those of natural prostaglandins, as demonstrated by their ability to mimic or antagonise the physiological effects of the natural prostaglandins in various biological preparations. In particular, certain compounds of formula (I) have been found to be potent mimetics of the antiplatelet aggregatory properties of prostaglandin E_1.



(I)

Z is hydrogen; one of Z^1 and Z^2 is represented by the group $—CH_2—X—X^1—X^2$;

wherein X is phenylene, *cis* —CH=CH— or $—CH_2—CH_2—$; X^1 is a covalent bond or a straight or branched alkylene chain having 1 to 6 carbon atoms optionally having one of its methylene groups replaced by oxa(—O—) provided that at least one carbon atom separates the oxa group from a —CH=CH— or —CO— group; and X^2 is selected from carboxyl, and alkoxycarbonyl;

and the other of Z^1 and Z^2 is represented by the group $—Y—Y^1—Y^2—Y^3$

wherein Y is $—CH_2—CH—$; Y^1 is carbonyl, methylene, methylene substituted by hydroxy or methylene substituted by hydroxy and alkyl; Y^2 is a covalent bond or straight or branched alkylene having 1 to 7 carbon atoms; Y^3 is hydrogen, hydroxy, alkoxy having 1 to 7, preferably 1 to 4, carbon atoms, benzyl, phenoxy or

benzyloxy, wherein each benzyl, phenoxy and benzyloxy may be substituted in the benzene ring by one or more groups selected from hydroxy, halo, nitro, amino, acylamino, alkenyl, alkoxy, phenyl and alkyl which may itself be substituted by one or more halo groups; provided that, when Y^2 is a covalent bond then Y^3 is not hydroxy when Y^1 includes hydroxy; or Y^2 is a covalent bond and Y^3 is a cycloalkyl having 4 to 7 carbon atoms as hereinafter defined.

Unless otherwise stated, in formula (I) and other formulae in this specification, alkyl moieties are selected from methyl, ethyl, propyl and butyl, including all isomers thereof.

For example, in the definitions of Y^1 and Y^2 the alkyl groups are preferably methyl; and the alkyl moiety of alkoxycarbonyl is desirably methyl or ethyl. Similarly alkylene groups have 2 to 4 carbon atoms for example vinyl.

In formula (I) cycloalkyl groups may be substituted by one or more alkyl groups, and also may have one or more of their hydrogens replaced by fluoro.

In a compound of formula (I) the bonding of the divalent phenylene groups may be *ortho, meta* or *para* and the oxa group is preferably adjacent the phenylene or when X is other than phenylene then X^1 may be $—CH_2—O—CH_2—$.

Included in the meaning of compounds of formula (I) are the salts corresponding to the carboxylic acids when X^2 is carboxyl, and the salts which may also be formed when Z is hydrogen. Particularly valuable salts for medical purposes are those having a pharmaceutically acceptable cation such as ammonium or that of an alkali metal e.g. sodium and potassium, an alkaline earth metal e.g. calcium or magnesium, or an organic base, particularly an amine such as ethanolamine. Salts having non-pharmaceutically acceptable cations are included within the ambit of this invention as useful intermediates to pharmaceutically acceptable salts, or the acids or esters of formula (I).

Except when there is clear indication to the contrary, formula (I) and other formulae in the specification embrace all stereoisomers represented therein. In particular such formulae include the enantiomeric forms, such mixtures as are designated racemates, and diastereoisomers.

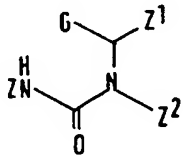
It has been found that compounds of formula (I) wherein

Z is hydrogen;

one of Z^1 and Z^2 is $—CH_2—X—X^1—X^2—$ wherein X and X^1 taken together form alkylene of 3 to 7 in particular 5 carbon atoms, and X^2 is alkoxycarbonyl, carboxyl or a salt thereof;

and the other of Z^1 and Z^2 is $—Y—Y^1—Y^2—Y^3—$ wherein Y, Y^1 and Y^2 are as hereinbefore defined and Y^3 is hydrogen, benzyl, or cycloalkyl of 4 to 7 carbon atoms; have particularly interesting prostaglandin-related properties. Within this definition are included the subclass wherein Z^1 is $—CH_2—X—X^1—X^2—$ as defined.

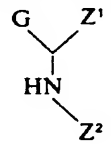
The compounds of formula (I) may be synthesised by any method known in the art for the synthesis of compounds of analogous structure. For example, they may be prepared from the corresponding derivatives of hydantoic acid of formula (II)



(II)

wherein G is carboxyl or a derivative thereof such as amide or ester in particular an alkyl ester, and each of Z, Z^1 and Z^2 has the same meaning as in formula (I), by cyclisation under acidic conditions or by heating alone. The reaction may be effected in the absence of a solvent, but if desired an inert solvent may be used, for example a hydrocarbon such as petrol. Alternatively, where G is alkoxycarbonyl, cyclisation may be effected in the presence of a suitable base, for example an alkoxide such as sodium ethoxide.

Compounds of formula (II) are conveniently prepared from an amino acid derivative of formula (III)



(III)

wherein G, Z^1 and Z^2 are as defined in formula (I) provided that G may also be cyano by reaction with cyanic acid or an alkyl iso-cyanate depending respectively on whether Z is hydrogen or alkyl.

When cyanic acid is used, the cyanic acid is conveniently produced *in situ* by the use of an alkali metal cyanate, e.g: potassium cyanate, and an acid which may be present as an acid addition salt of the compound of formula (III) or a free acid of formula (III) wherein for example X^2 is hydrogen. Alternatively an equivalent amount of mineral acid or an organic acid may be added to the reaction medium. The reaction may proceed in the absence of a solvent but desirably an inert solvent is used which is preferably polar such as water or a mixture of water with acetone dimethylformamide, dimethylsulphoxide or a lower alkanol such as ethanol or it may be a hydrocarbon, an ether or halogenated hydrocarbon such as chloroform. Where desired, for example if no solvent is used, the reaction may be promoted by heating the reactants.

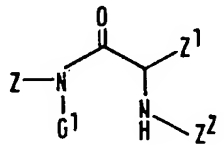
Similar reaction conditions may be used when an alkyl *iso*-cyanate is used except that it is unnecessary to provide an equivalent amount of acid, as an acid addition salt or otherwise, in the reactants.

Instead of using a cyanate or isocyanate, a compound of formula (III) may be reacted with urea, nitrourea or an *N*-alkylurea as appropriate. A solvent is not essential but if desired an inert solvent such as one mentioned above may be used, and the reaction is preferably effected at an elevated temperature, for example from 100° to 125°C but temperatures upto 150°C may be employed.

In the above described synthesis, the intermediates of formula (II) need not be isolated from the reaction mixture and may be converted directly to compounds of formula (I) under the described reaction conditions.

Intermediates of formula (III) are disclosed in our co-pending UK application No. 917/76 and may be conveniently prepared according to the methods described therein.

Hydantoins of formula (I) may also be prepared by cyclisation of a compound of formula (VII)

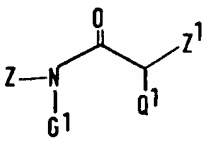


(VII)

wherein Z, Z^1 and Z^2 are as defined in formula (I) and G^1 is carboxyl or a reactive derivative thereof such as alkoxycarbonyl e.g. ethoxycarbonyl. Compounds of formula (VII) may be cyclised under similar conditions as a compound of formula (II) and conveniently the method used to prepare a compound of formula (VII) is chosen such that the prevailing reaction conditions permit spontaneous cyclisation.

For example, the intermediates of formula (VII) may be prepared by reacting a compound of formula (V) with a compound of formula (VIII)

$$Q^2—Z^2 \qquad \text{(V)}$$



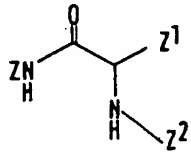
(VIII)

wherein one of Q^1 and Q^2 is halogeno, preferably chloro or bromo and the other is amino and each of Z, Z^1, Z^2 and G^1 have the same meaning as in formula

(VII). The reaction may be effected by admixture of the reactants or optionally an inert solvent is used and the mixture is heated. Suitable solvents include alkanols, ethers, hydrocarbons and halogenated hydrocarbons.

The compounds of formula (VIII) may themselves be made by reacting an appropriate carbamic acid derivative, for example an alkyl ester, with a compound of formula (IV), using techniques known to those skilled in the art.

In a method related to those described hereinbefore, the hydantoins of formula (I) may be prepared by reacting a compound of formula (IX)

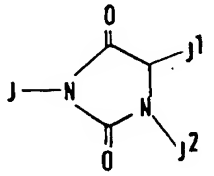


(IX)

wherein each of Z, Z^1 and Z^2 has the same meaning as in formula (I) with a carbonic acid derivative. Any carbonic acid derivative known to those skilled in the art as appropriate may be used, for example phosgene, diphenylcarbonate or an alkyl haloformate such as ethyl chloroformate. The reaction is desirably effected in the presence of a base, for example an amine such as triethylamine or di-*iso*-propyl ethylamine, and using an inert aprotic solvent such as toluene, dimethylformamide or an ether such as diethylether. The reaction may be carried out at room temperature but if desired the reaction mixture may be heated.

The intermediates of formula (IX) may be made using methods analogous to those referred to above for the preparation of compounds of formula (III).

The hydantoins of formula (I) may also be prepared by alkylation, using an alkylating agent which may be designated as a reactive ester derivative of an alcohol J^3.OH, of a compound of formula (X)



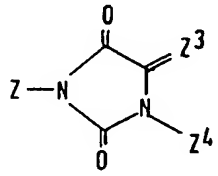
(X)

wherein J is hydrogen, J^1 is hydrogen or Z^1, J^2 is hydrogen or Z^2 and J^3 is Z^1 or Z^2, provided that one of J^1 and J^2 is hydrogen and J^3 does not have the same value as J^1 or J^2; in the definition of J^1, J^2 and J^3 each of Z^1 and Z^2 has the same meaning as in formula (I). Suitable reactive ester derivatives include chloride, bromide, iodide and sulphonates such as *p*-toluenesulphonate, methanesulphonate and benzenesulphonate. The alkylation may be effected using reaction conditions which are known in the art to be suitable, for example in the presence of a base such as an alkalimetal hydride, alkali metal amide, or alkali-metal alkoxide, typically sodium hydride or a sodium alkoxide e.g. sodium methoxide.

The reaction is conveniently carried out in an inert solvent which simply acts as a diluent for the reactants such as toluene, dioxan, ether, dimethylformamide, tetrahydrofuran, dimethylsulphoxide or acetonitrile or when the base is an alkali metal alkoxide then the corresponding alkanol may be used.

The compounds of formula (X) may further be prepared by adaptation of methods already known in the art (see for example Chemical Reviews (1950) *46*, p. 403—425).

A further preparation of compounds of formula (I) is by reduction of a corresponding unsaturated compound of formula (XI)

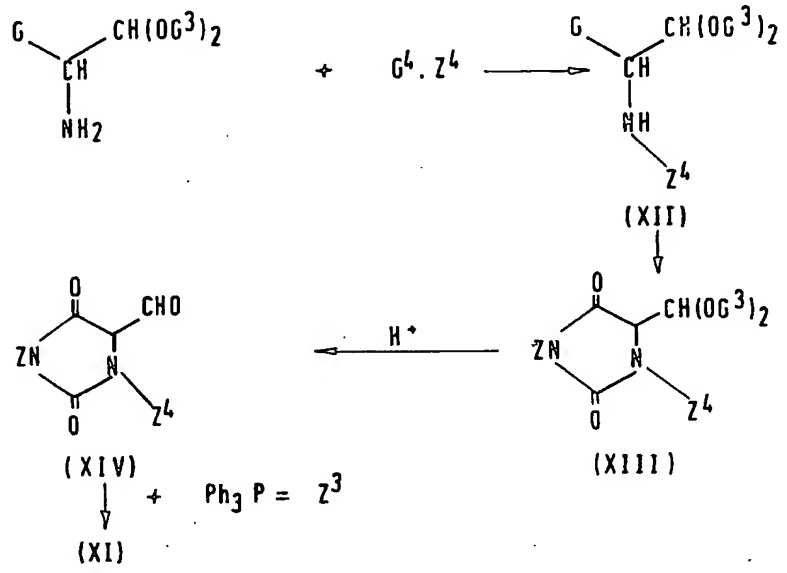


(XI)

wherein either Z^3 is $=CH—CH_2—Y^1—Y^2—Y^3$ and Z^4 is $—CH_2—X—X^1—X^2$ or Z^3 is $=CH—X—X^1—X^2$ and Z^4 is $—Y—Y^1—Y^2—Y^3$ in which each of X to X^2 and Y to Y^3 is as defined in formula (I), with a suitable reducing agent.

A suitable reducing agent is stannous chloride which may be used as an aqueous solution optionally in the presence of dilute mineral acid or catalytic hydrogenation may be effected in the presence of for example Raney nickel, platinum, palladium, ruthenium or rhodium. The choice of reducing agent in a given situation will of course be dictated by the presence of other reactive groups in the molecule which may themselves be susceptible to reduction.

The intermediates of formula (XI) may be prepared by the following series of reactions:



In the above formulae Z, Z^3, Z^4 and G have the same meanings as in formulae (XI) and (III) respectively, G^3 is alkyl for example *n*-butyl and G^4 is halo such as bromo. The formation of (XIII) is analogous to the ring closure involving a compound of formula (II) and compounds of formula (XIV), are prepared using concentrated mineral acid such as hydrochloric acid.

In the synthesis of hydantoins of formula (I) having a hydroxy group in a side chain it may be desirable to protect this during the course of the reaction. This may be readily effected in known manner using a protecting group such as acyl, aroyl, tetrahydropyran-2-yl, 1-ethoxyethyl or aralkyl, for example benzyl.

Removal of protecting groups may be carried out by appropriate methods known to those skilled in the art: for example an acyl group may be removed by acid or base hydrolysis, and a benzyl group by reductive cleavage.

Furthermore a ketone of formula (I) wherein Y^1 is carbonyl may be converted to the corresponding secondary alcohol by reduction with a suitable reducing agent, such as sodium borohydride. Also, an alcohol of formula (I) wherein Y^1 is —CH.OH— may be oxidised to the corresponding ketone using Jones' reagent, acid dichromate or any other suitable reagent.

Similarly where the compounds of formula (I) have a C≡C or CH=CH bond these may be converted by conventional hydrogenation techniques, for example using a Lindlar type or Adams catalyst, to the corresponding ethylenic or saturated compounds as appropriate.

The hydantoins of formula (I) have an asymmetric 5-carbon atom, and a further asymmetric centre is present in those compounds wherein Y^1 includes a hydroxyl group. Such alcohols therefore exist as four isomers which are separable by thin layer chromatography or high performance liquid chromatography into two diastereomers, each of which is a racemic mixture of two isomers. On separation of the diastereomers, one diastereomer may be converted to a mixture of the four

isomers by treatment with a base, such as an alkali metal hydroxide, and subsequently re-separated to provide two diastereomers. Repeated use of this technique enables the effectual conversion of one diastereomer to the other; this may be desirable when one diastereomer has a biological activity preferred to the other.

The corresponding alcohols of formula (III) also exist in four isomeric forms. If desired, these may be separated into two epimers and subsequent cyclisation to a compound of formula (I) retains the stereochemical configuration.

In all of the foregoing chemical procedures it is of course evident that the choice of reactant will be dictated in part by the functional groups present in the substrate, and where necessary reactants having an appropriate selectivity of action must be used.

The hydantoins of formula (I) are of value in having pharmacological properties related to those of natural prostaglandins; that is, the hydantoins mimic or antagonise the biological effects of members of the prostaglandin (PG) 'A', 'B', 'C', 'D', 'E' and 'F' series. For example, hydantoins of formula (I) have been found to mimic the antiaggregatory effect of PGE_1 on blood platelets, and to antagonise the contraction induced by PGE_2 or PGF_2 on smooth muscle taken from the rat stomach, rat colon, chick rectum and guinea pig trachea. In general, antagonistic properties, as opposed to mimetic, have been observed when using larger doses of the hydantoins. The pharmacological profile, by which is meant the relative activities, mimitic or antagonistic, compared with the natural prostaglandins, will of course vary depending on the specific hydantoin under consideration.

By reason of their prostaglandin-related properties, the hydantoins of formula (I) are useful in the pharmacological characterisation and differentiation of the biological activities of the natural prostaglandins and their 'receptors'. The further understanding of the physiological role of prostaglandins is of course valuable in the search for new and improved therapeutic substances.

The hydantoins of formula (I) are also of value as therapeutic agents. In particular hydantoins such as those described previously as having a potent anti-aggregatory effect on blood platelets are useful whenever it is desired to inhibit platelet aggregation or to reduce the adhesive character of platelets, and may be used to treat or prevent the formation of thrombi in mammals, including man. For example, the compounds are useful in the treatment and prevention of myocardial infarcts, to treat and prevent thrombosis, to promote patency of vascular grafts following surgery, and to treat complications of arteriosclerosis and conditions such as atherosclerosis, blood clotting defects due to lipermia, and other clinical conditions in which the underlying aetiology is associated with lipid imbalance or hyperlipidemia. A further use for such compounds is as an additive to blood and other fluids which are used in artificial extra-corporeal circulation and perfusion of isolated body portions.

A group of compounds which have been found particularly valuable as inhibitors of platelet aggregation are those of formula (I) wherein Z is hydrogen; Z^1 is carboxyalkyl wherein the alkyl moiety has 3 to 9 carbon atoms; and Z^2 is a group $-(CH_2)_2.CH.OH.Y^2.Y^3$ wherein Y^2 is branched alkylene having a tertiary carbon atom adjacent the hydroxy-substituted carbon and Y^3 is as defined in formula (I).

Within this group of compounds, those wherein Z^1 is carboxyhexyl and Y^3 is cycloalkyl having 4 to 7 carbon atoms have been found especially active.

It has also been found that hydantoins of formula (I) cause relaxation of vascular smooth muscle in a similar way as do members of the prostaglandin 'A' and 'E' series. An example of such compounds is 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyloctyl)hydantoin. Compounds relaxing vascular smooth muscle are capable of inducing vasodilation and therefore have antihypertensive properties and are useful in lowering blood pressure in mammals, including man, and may be used alone or in combination with a β-adrenoceptor blocking agent or another antihypertensive substance for the treatment of all grades of hypertension including essential, malignant and secondary hypertension.

The compound 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyl)hydantoin also mimics the effect of PGE_1 of antagonising histamine induced broncho-constriction. The hydantoins of formula (I) having this property may be used in the treatment or prophylaxis of bronchial asthma and bronchitis by alleviating the bronchoconstriction associated with this condition.

Hydantoins of formula (I), such as 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl) - hydantoin, 5 - (6 - carboxyhexyl) - 1 - (3 - oxo - octyl)hydantoin and 5 - (6 - carboxyhexyl) - 1 - (4 - phenoxybutyl)hydantoin, which inhibit

pentagastrin-induced gastric acid secretion and reduce the formation of aspirin-induced gastric lesions in rats are useful in reducing excessive gastric secretion, reducing and avoiding gastro-intestinal ulcer formation and accelerating the healing of such ulcers already present in the gastrointestinal tract whether such ulcers arise spontaneously or as a component of polyglandular adenoma syndromes.

Intravenous infusions of certain hydantoins of formula (I), typically 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin, to dogs has been found to increase urine volume indicating a potential utility for such compounds as diuretic agents, the uses of which include the treatment of oedema for example oedema associated with heart failure, liver failure or kidney failure in man or other mammals.

A further use for hydantoins of formula (I) which mimic the uterine smooth muscle effects of PGE_2 and $PGF_{2\alpha}$ is as antifertility agents, in particular as abortifacients.

The amount of a compound of formula (I) required to achieve the desired biological effect will of course depend on a number of factors, for example, the specific compound chosen, the use for which it is intended, the mode of administration, and the recipient. In general, a daily dose may be expected to lie in the range of from 1 μg to 20 mg per kilogram bodyweight. For example, an intravenous dose may lie in the range of from 5 μg to 1 mg/kg which may conveniently be administered as an infusion of from 0.01 to 50 μg per kilogram per minute. Infusion fluids suitable for this purpose may contain from 0.001 to 100, for example from 0.01 to 10 μg per millititre. Unit doses may contain from 10 μg to 100 mg of a compound of formula (I), for example ampoules for injection may contain from 0.01 to 1 mg, and orally administrable unit dose formulations such as tablets or capsules may contain from 0.1 to 50, for example 2 to 20 mg.

More specifically, when a compound of formula (I) is used to inhibit platelet aggregation it is generally desirable to achieve a concentration in the appropriate liquid, whether it be the blood of a patient or a perfusion fluid, of from 1 μg to 10 mg, for example from 10 μg to 1 mg, per liter.

The abovementioned doses refer to the acids and esters, of formula (I); where a salt is used, the dose should be taken as referring to the corresponding anion.

For use in the treatment or prophylaxis of the conditions referred to above, while the hydantoin compounds may be used as the raw chemical they are preferably presented with an acceptable carrier therefor as a pharmaceutical formulation. The carrier must of course be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The carrier may be a solid or a liquid, and is preferably formulated with a hydantoin compound as a unit-dose formulation, for example a tablet, which may contain from 0.05% to 95% by weight of the hydantoin compound. Other pharmacologically active substances may also be present in formulations of the present invention as indicated above. The hydantoin compounds may be incorporated in the formulations either in the form of the acid or the salt or ester thereof, and the formulations may be prepared by any of the well-known techniques of pharmacy consisting essentially of admixture of the components of the formulation.

The formulations include those suitable for oral, rectal, topical (buccal—e.g. sub-lingual), the parenteral (that is subcutaneous, intramuscular and intravenous) administration, although the most suitable route in any given case will depend on the nature and severity of the condition being treated, and on the nature of the hydantoin compound.

Formulations suitable for oral administration may be presented at discrete units such as capsules, cachets, lozenges or tablets each containing a predetermined amount of hydantoin compound; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; as an oil-in-water emulsion; or as a water-in-oil liquid emulsion. Such formulations may be prepared by any of the methods of pharmacy but all methods include the step of bringing into association the hydantoin compound with the carrier which constitutes one or more accessory ingredients. In general they are prepared by uniformly and intimately admixing the hydantoin compound with liquid or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation. For example a tablet may be prepared by compression or moulding a powder or granules of the hydantoin compound, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a

suitable machine, the hydantoin compound in a free-flowing form such as a powder or granules optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent(s). Moulded tablets may be made by moulding in a suitable machine the powdered hydantoin compound moistened with an inert liquid diluent.

Formulations suitable for buccal (sub-lingual) administration include lozenges comprising a hydantoin compound in a flavoured basis, usually sucrose and acacia or tragacanth; and pastilles comprising a hydantoin compound in an inert basis such as gelatin and glycerin; or sucrose and acacia.

Formulations of the present invention suitable for parenteral administration conveniently comprise sterile aqueous preparations of a hydantoin compound, which preparations are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although administration may also be effected by means of subcutaneous or intramuscular injection. Such preparations may be conveniently prepared by admixing the hydantoin compound with water and rendering the product sterile and isotonic with the blood.

Formulations suitable for rectal admistration are preferable presented as unit-dose suppositories. These may be prepared by admixture of the hydantoin compound with one or more of the conventional solid carriers, for example cocoa butter, and shaping of the resulting mixture.

It will be appreciated from the foregoing that what we will claim may comprise, principally and not exclusively, for example:—

(a) The novel compounds of formula (I) as hereinabove defined.

(b) A method for the preparation of the novel compounds of formula (I) as hereinabove described.

(c) A pharmaceutical formulation comprising a compound of formula (I) in association with a pharmaceutically acceptable carrier therefor, and methods for the preparation of such formulations.

(d) A method for lowering blood pressure in a mammal excluding man which comprises administration to the mammal of an effective hypotensive, non-toxic amount of a compound of formula (I).

(e) A method for the treatment or propylaxis of thrombosis in a mammal or mammalian tissue, excluding human, which comprises administration of a non-toxic, effective anti-thrombatic amount of a compound of formula (I).

(f) A method for inducing vasodilation in a mammal, excluding man, comprising administration to said mammal of a non-toxic effective vasodilatory amount of a compound of formula (I).

(g) A method for the treatment or prophylaxis of gastric lesions in a mammal excluding man comprising administration to said mammal of a non-toxic effective prophylactic or therapeutic amount of a compound of formula (I).

(h) A method for inducing bronchodilation in a mammal, excluding man, comprising administration to said mammal of a non-toxic, effective bronchodilatory amount of a compound of formula (I).

(i) A method for the treatment or prophylaxis of an allergic condition in a mammal, excluding man, comprising administration to said mammal of a non-toxic effective prophylactic or therapeutic amount of a compound of formula (I).

(j) A method of inducing abortion of a foetus in a mammal excluding human comprising administration to said mammal of a non-toxic effective abortifacient amount of a compound of formula (I).

(k) A method of inducing infertility in a mammal excluding human comprising administration to said mammal of a non-toxic effective contraceptive amount of a compound of formula (I).

Reference Example A

5 - (6 - Ethoxycarbonylhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyl - 5 - phenylpentyl)hydantoin and the corresponding acid

A solution of diethyl 2 - [(3 - hydroxy - 4,4 - dimethyl - 5 - phenylpentyl)amino]nonanedioate prepared according to Example 1C of our co-pending UK application No. 9171/76 (Serial No. 1595693) (8.45 g) in ethanol (37.6 ml) and 2N-hydrochloric acid (18.8 ml) was stirred and cooled in ice during the dropwise addition of a solution of potassium cyanate (3.05 g) in water (5.6 ml). The mixture was allowed to stand at room temperature for 18 hours, then the alcohol was evaporated, water was added and the insoluble oil was extracted with ether. The dried ether solution was evaporated to leave a viscous oil which was heated on

the steam bath for 6 hours to give 5 - (6 - ethoxycarbonylhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyl - 5 - phenylpentyl)hydantoin as a viscous pale yellow oil.

This ester was added to a mixture of 2N-sodium hydroxide (25 ml) and water (60 ml) and the resulting cloudy solution was left at room temperature for 2 hours. The solution was washed with diethyl ether and the clear alkaline solution was acidified with 2N-hydrochloric acid and the precipitated oil was extracted with ether. Evaporation of the dried ether solution gave a viscous oil (6.8 g) which was chromatographed on a column of silica gel to give 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyl - 5 - phenylpentyl) - hydantoin as a colourless viscous oil which solidified, m.p. *ca.* 115°C, shrinking from *ca.* 90°C being a mixture of diastereomers. Recrystallisation several times from a mixture of ethyl acetate and light petroleum (b.p. 60—80°C) gave one of the diastereomers as small needles, m.p. 135—137°C.

EXAMPLE 1:

Preparation of 5-(6-carboxyhexyl)-1-(3-hydroxyoctyl)hydantoin

A. 5 - (6 - Carboxyhexyl) - 1 - (3 - (tetrahydropyran - 2 - yloxy)octyl)hydantoin

To a solution of diethyl 2 - (3 - (tetrahydropyran - 2 - yloxy)octylamino)nonanedioate prepared according to Example 2A of our co-pending UK application No. 9171/76 (Serial No. 1595693 (7.8 g) in ethanol (32 ml) was added a solution of potassium cyanate (3.0 g) in water (6 ml). The resulting suspension was stirred and cooled during the gradual addition of 2*N*-hydrochloric acid (16.7 ml). The solution was allowed to stand at room temperature for 22 hours, most of the ethanol was evaporated, water was added, and the insoluble oil was extracted with ether. The ether solution was washed with water, dried over magnesium sulphate, and evaporated. The yellow oil so obtained (8.0 g) was dissolved in light petroleum (b.p. 60—80°C) and the solution was refluxed for 4 hours, evaporated to dryness, and the residual oil was heated on the steambath for 2 hours to give 5 - (6 - ethoxycarbonylhexyl) - 1 - (3 - (tetrahydropyran - 2 - yloxy)octyl)hydantoin as a yellow oil (7.3 g), which was used without further purification.

A solution of the ester (6.2 g) in 0.5*N*-sodium hydroxide solution (80 ml) was allowed to stand at room temperature for 2¼ hours, after which the solution was washed with diethyl ether, the aqueous layer was acifidied with 2*N*-hydrochloric acid, and the precipitated oil was extracted with diethyl ether. The washed and dried ether extract was evaporated to give 5 - (6 - carboxyhexyl) - 1 - (3 - (tetrahydropyran - 2 - yloxy)octyl)hydantoin as a yellow oil.

B. 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin

This tetrahydropyranyloxy-compound (3.55 g) was dissolved in tetrahydrofuran (28 ml) and 5*N*-hydrochloric acid (7 ml) and the solution was left at room temperature for 3¼ hours, and then refluxed for 30 minutes. Most of the solvent was evaporated, water was added, and the insoluble oil was extracted with diethyl ether. The ether solution was washed with water, dried over magnesium sulphate and evaporated to give 3.15 g. of viscous yellow oil. The oil was purified by chromatography on a column of silica gel, elution first with chloroform and then with a mixture of chloroform and methanol (19:1 v/v) giving 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin as a very viscous almost colourless oil, 80.89(3H, triplet, $-CH_3$), 2.34(2H, triplet, $-CH_2-CO_2H$), 2.9—4.2(4H, complex, $-CH_2-N$, $CH-N$, $CH-OH$), *ca.* 5.6(2H, broad, exchangeable, $-CO_2H$, —OH), *ca.* 9.0(1H, broad, exchangeable, NH).

C. Separation of Diastereomers

The hydantoin resulting from the above described preparations was a viscous oil which by use of HPLC on a column of silica with a mixture of chloroform, methanol and acetic acid (97:2.5:0.5) as solvent was separated into two diastereomers, both of which formed small colourless needles of m.p. 76—78°C and 63—65°C respectively.

The same diastereomers were prepared by cyclisation of the corresponding diastereomers of formula (III). That is, the mixture of diastereomers of diethyl 2 - [(3 - hydroxyoctyl)amino]nonanedioate, prepared as in Example 1 of our co-pending UK application No. 9171/76 (Serial No. 1595693) were separated as in Example 2D of our co-pending UK application No. 9171/76 (Serial No. 1595693) to give one of the diastereomers (A) of diethyl 2 - [(3 - hydroxyoctyl)amino]nonanedioate as a colourless oil and the almost pure second

diastereomer (B) of diethyl 2 - [E - hydroxyoctyl)amino]nonanedioate as a colourless oil.

By the method described in Example A, the above diastereomer (A) was converted into a single diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin, which crystallised from a mixture of ethyl acetate and light petroleum (b.p. 60—80°) as small colourless needles, m.p. 63—65°.

Similarly the above diastereomer (B) was converted into the second diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin which crystallised from ethyl acetate-light petroleum (b.p. 60—80°) as small colourless needles, m.p. 76—78°.

E. Interconversion of the diastereomers

A solution of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin (diastereomer of m.p. 76—78°) (100 mg) in *N*-sodium hydroxide solution (3 ml) was allowed to stand at room temperature for 19 hours. The solution was acidified and extracted with diethyl ether, and the ether extract was washed with water, dried and evaporated to leave a viscous oil. By means of high performance liquid chromatography this oil was separated into the two diastereomers of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin, m.p. 76—78°C identical with the starting material (*ca.* 40 mg) and m.p. 63—65°C (*ca.* 40 mg) identical with the diastereomer (A) described above.

In similar fashion, the diastereomer of m.p. 63—65°C was converted into a mixture of approximately equal quantities of itself with the diastereomer of m.p. 76—78°C, and the pure diastereomers were isolated by means of high performance liquid chromatography.

EXAMPLES 2 TO 27

By a series of reactions analogous to that described in Reference Example A, using the appropriate intermediates as described in Examples 3 to 27 of our co-pending UK application No. 9171/76 (Serial No. 1,595,693) were prepared:

the following hydantoins of formula (I) which where indicated were separated by HPLC to provide two diastereomers having the stated melting points, respectively:

2. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxypentyl)hydantoin, a colourless oil, diastereomers 71—73° and 56—58°;

3. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethylpentyl)hydantoin, diastereomers 114—115° and 144—146°;

4. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - methylpentyl)hydantoin, m.p. *ca.* 70—80°, diastereomers 73—76° and 110—111°;

5. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxynonyl)hydantoin, a viscous oil;

6. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - methyloctyl)hydantoin, a viscous oil;

7. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxydecyl)hydantoin, a viscous oil, diastereomers 68—70° and 82—83°;

8. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyloctyl)hydantoin as colourless crystals, m.p. 90—98°, one diastereomer isolated by crystallisation from ethyl acetate m.p. 103—104°;

9. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - ethylhexyl)hydantoin, m.p. 70—80°, diastereomers 82—84° and 120—122°;

10. 5 - (6 - carboxyhexyl) - 1 - (3 - cyclobutyl - 3 - hydroxypropyl)hydantoin, diastereomers 114—116° and 103—105°;

11. 5 - (6 - carboxyhexyl) - 1 - (3 - cyclopentyl - 3 - hydroxypropyl)hydantoin, diastereomers 116—117° and 97—99°;

12. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyl - 5 - *m* - trifluoromethylphenylpentyl)hydantoin, diastereomers 118—120° and 145—147°;

13. 5 - (6 - carboxyhexyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin, diastereomers 96—98° and 124—126°;

14. 5 - (6 - carboxyhexyl) - 1 - (3 - cycloheptyl - 3 - hydroxypropyl)hydantoin, m.p. *ca.* 70—76°, diastereomers 107—109° and 107—109°;

15. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - phenylbutyl)hydantoin, diastereomers 102—104° and 61—63°;

16. 5 - (3 - carboxypropyl) - 1 - (3 - hydroxyoctyl)hydantoin, diastereomers both forming colourless viscous oils;

17. 5 - (8 - carboxyoctyl) - 1 - (3 - hydroxyoctyl)hydantoin, diastereomers 57—60° and 69—71°;

18. 5 - (3 - carboxymethoxybenzyl) - 1 - (3 - hydroxyoctyl)hydantoin, a colourless meringue;

19. 5 - (3 - carboxymethoxybenzyl) - 1 - (3 - hydroxy - 4,4 - dimethylpentyl)hydantoin; diastereomers of the corresponding ethyl ester m.p. 100—103° & 151—154°;

20. 5 - (3 - (2 - carboxyethylbenzyl)) - 1 - (3 - hydroxyoctyl)hydantoin; one diastereomer m.p. 82—86°;

21. 5 - (3 - (2 - carboxyethylbenzyl)) - 1 - (3 - cyclobutyl - 3 - hydroxypropyl)hydantoin; one diastereomer 118—121°;

22. 5 - (3 - (2 - carboxyethylbenzyl)) - 1 - (3 - cyclopentyl - 3 - hydroxypropyl)hydantoin; one diastereomer 140—143°;

23. 5 - (3 - (2 - carboxyethylbenzyl)) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin;

24. 5 - (4 - carboxymethoxybutyl) - 1 - (3 - hydroxyoctyl)hydantoin; and

25. 5 - (4 - carboxymethoxybutyl) - 1 - (3 - cyclopentyl - 3 - hydroxypropyl)hydantoin;

all of which were obtained via the corresponding ethyl ester.

EXAMPLE 28

Preparation of 5-(6-carboxyhexyl)-1-(3-oxooctyl)hydantoin

Diethyl 2 - (3 - oxooctylamino)nonanedioate (7.7 g) prepared by the method described in Example 2A of our co-pending UK application No. 9171/76 (Serial No. 1595693 was treated with potassium cyanate and hydrochloric acid to give 5 - (6 - ethoxycarbonylhexyl) - 1 - (3 - oxo - octyl)hydantoin. Hydrolysis of this ester using sodium hydroxide solution gave 5 - (6 - carboxyhexyl) - 1 - (3 - oxooctyl) - hydantoin as a viscous oil, which crystallised to a low melting solid.

Example 27

Preparation of 5-(6-carboxyhexyl)-1-(5-phenylpentyl)hydantoin

A solution of diethyl 2 - [(5 - phenylpentyl)amino]nonanedioate hydrobromide (4.86 g) prepared according to Example 28 of our co-pending application No. 9171/76 (Serial No. 1595693) in ethanol (20 ml) and 2N-hydrochloric acid (5 ml) was cooled in ice and stirred during the gradual addition of a solution of potassium cyanate (1.62 g) in water (5 ml), after which the solution was allowed to stand at room temperature for 18 hours. The alcohol was evaporated, water was added, the insoluble oil was extracted with diethyl ether, and the ethereal extract was dried and evaporated to leave a pale yellow oil. This material was heated on the steam bath for 6 hours to give 5 - (6 - ethoxycarbonylhexyl) - 1 - (5 - phenylpentyl)hydantoin.

The foregoing ester (4.0 g) was hydrolysed by treatment with dilute sodium hydroxide solution and the product was purified by chromatography on silica gel, to give 5 - (6 - carboxyhexyl) - 1 - (5 - phenylpentyl)hydantoin crystallising from ethyl acetate-light petroleum (b.p. 60—80°C) in colourless prismatic needles, m.p. 90—92°C.

Examples 28 to 34

By a series of reactions analogous to that described in Example 26 using the appropriate intermediates according to Examples 29 to 35 of our co-pending UK application were prepared, respectively:

28a. 5 - (6 - ethoxycarbonylhexyl) - 1 - octylhydantoin, m.p. 46—48°;

28b. 5 - (6 - carboxyhexyl) - 1 - octylhydantoin, m.p. 88—89°;

29. 5 - (6 - carboxyhexyl) - 1 - (4 - propoxybutyl)hydantoin, m.p. 72—74°;

30. 5 - (6 - carboxyhexyl) - 1 - (4 - phenoxybutyl)hydantoin, m.p. 88—90°;

31. 5 - (6 - carboxyhexyl) - 1 - (4 - *m* - trifluoromethyl-phenoxybutyl)hydantoin, m.p. 51—54°;

32. 5 - (6 - carboxyhexyl) - 1 - (3 - *m* - tolyloxypropyl)hydantoin, a colourless viscous oil;

33. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxypropyl)hydantoin, m.p. 111—113°; and

34. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - methyloctyl)hydantoin, a viscous oil.

EXAMPLE 35

Preparation of 1-(6-Carboxyhexyl)-5-octylhydantoin

Ethyl 2 - (6 - ethoxycarbonylhexylamino)decanoate (7.4 g) prepared according to Example 36 of our co-pending application No. 9171/76 (Serial No. 1595693 was reacted with potassium cyanate and hydrochloric acid to give 1 - (6 - ethoxycarbonylhexyl) - 5 - octylhydantoin which formed colourless crystals, m.p. 68—70°C, from light petroleum (b.p. 60—80°C).

This ester (4.0 g) was hydrolysed with sodium hydroxide solution to give 1 - (6 - carboxyhexyl) - 5 - octylhydantoin which crystallised from a mixture of ethyl acetate and light petroleum (b.p. 60—80°C) as colourless needles, m.p. 65—66°C.

Example 36

Preparation of 5-(6-Carboxyhexyl)-1-(3-hydroxyoctyl)hydantoin

5 - (6 - carboxyhex - 2 - ynyl) - 1 - (3 - hydroxyoctyl)hydantoin prepared according to Example 13 of our co-pending UK application No. 11276/80 (Serial No. 1595695) (one of the diastereomers (TLC, Rf. 0.38)) was catalytically hydrogenated to the corresponding 5 - (6 - carboxyhex - 2(Z) - enyl) - 1 - (3 - hydroxyoctyl)hydantoin and subsequently to the corresponding saturated compound which was found to be identical with the title compound of Example 1.

Example 37

Preparation of 1-(6-carboxyhexyl)-5-(3-hydroxyoctyl)hydantoin

A. 2 - (Dibutoxymethyl)glycine ethyl ester

N - 2 - Formylglycine ethyl ester was *C*-formylated using a method based on that described by Harman and Hutchinson in J. Org. Chem. 1975 *40*, 3474 and the resulting compound converted to 2 - (dibutoxymethyl)glycine ethyl ester using the method described in "Chemistry of Penicillin", Eds. H. T. Clarke *et al.*, published by Princetown University Press, New Jersey, 1949, p. 517.

B. 1 - (6 - Carboxyhexyl)hydantoin - 5 - carboxaldehyde

A mixture of 2 - (dibutoxymethyl)glycine ethyl ester (2.0 g.) with ethyl 7-bromoheptanoate (1.82 g.) was heated under nitrogen in a bath at 100°C for 3 hr. to give crude ethyl 7 - ((2,2 - dibutoxy - 1 - ethoxycarbonylethyl)amino)heptanoate hydrobromide. A stirred solution of 3.28 g. of this hydrobromide in ethanol (13 ml) was cooled in ice-water and treated with a solution of potassium cyanate (1.34 g) in water (4 ml), followed by 2*N* aqueous hydrochloric acid (3.63 ml); the cooling bath was removed and stirring was continued at room temperature for 22 hr. The ethanol was evaporated *in vacuo*, the residue was shaken with water and diethyl ether, and the ethereal solution was separated, washed with water and dried over magnesium sulphate ($MgSO_4$); removal of the ether left an oil which was heated under nitrogen at 100°C for 3 hr., to give 5 - dibutoxymethyl - 1 - (6 - ethoxycarbonylhexyl)hydantoin (2.94 g.). This was stirred in diethyl ether (6 ml.) with water (48 ml) and *N* aqueous sodium hydroxide (24.9 ml) at room temperature for 1¼ hr. and, after the addition of more diethyl ether (50 ml), the aqueous phase was separated, cooled (ice-H_2O), stirred with fresh diethyl ether and acidified to Congo Red with *N* aqueous hydrochloric acid. The ethereal solution of carboxylic acid was thrice washed with water, dried ($MgSO_4$), and evaporated, to leave 1 - (6 - carboxyhexyl) - 5 - dibutoxymethylhydantoin (2.15 g.) as a gum. When 1.89 g. of the latter were cooled in ice-water and stirred with concentrated aqueous hydrochloric acid (8.5 ml.), the resulting solution gave place spontaneously to a suspension of colourless crystals. The suspension was set aside at room temperature for 1¼ hr., diluted with water (10 ml.) and set aside 15 min.; the crystals were then collected, washed with water, dried *in vacuo*, suspended in ether (3 ml.), and collected again, to give 1 - (6 - carboxyhexyl)hydantoin - 5 - carboxaldehyde (0.74 g.), m.p. 223.5—225°C (Found: C. 51.86— H, 6.66; N, 10.62. $C_{11}H_{16}N_2O_5$ required C, 51.56; H, 6.29; N, 10.93%). In dimethyl sulphoxide-d_6, this compound exists predominantly as the masked aldehyde, 1 - (6 - carboxyhexyl) - 5 - hydroxymethylene - hydantoin.

C. 1 - (6 - Carboxyhexyl) - 5 - ((*E*) - 3 - oxo - octylidene)hydantoin

A mixture of 1 - (6 - carboxyhexyl)hydantoin - 5 - carboxaldehyde (20 mg.) with 2 - oxoheptylidene - triphenylphosphorane (59 mg.) (see J. Org. Chem. (1972) *37*, 1818) and 1 drop of benzene was heated under nitrogen at 100°C for 35 min., and the resulting gum was taken up in ethyl acetate. The product was extracted into dilute aqueous sodium bicarbonate, the extract was washed with ethyl acetate and

acidified to Congo Red with *N* aqueous hydrochloric acid, and the liberated carboxylic acid was extracted into ether. The ethereal solution was washed with water, dried ($MgSO_4$), and evaporated, to give a gum (25 mg.) which was identified by ^1H n.m.r. spectroscopy (characteristic signals at δ5.72 (1H, triplet, =CH—) and 3.93 (2H, doublet, =CH—CH_2—CO) with j 7.1 Hz, in deuterochloroform) as 1 - (6 - carboxyhexyl) - 5 - ((*E*) - 3 - oxo - octylidene)hydantoin.

D. 1 - (6 - Carboxyhexyl) - 5 - (*E*) - 3 - hydroxyoctylidene)hydantoin

A stirred solution of 1 - (6 - carboxyhexyl) - 5 - ((*E*) - 3 - oxo - octylidene)hydantoin (20 mg.) in H_2O (1.5 ml. 1 containing a slight excess of sodium bicarbonate was treated with sodium borohydride (5 mg.). After 60 min., the solution was acidified to Congo Red with *N* aqueous hydrochloric acid, the liberated carboxylic acid was extracted into ethyl acetate, and the ethyl acetate solution was thrice washed with water and dried ($MgSO_4$). Evaporation of the ethyl acetate left a pale yellow gum (14 mg.) which was identified by ^1H n.m.r. spectroscopy (characteristic signal at δ5.61 (1H, triplet =CH—, J 7.1 Hz) in deuterochloroform) as 1 - (6 - carboxyhexyl) - 5 - ((*E*) - 3 - hydroxyoctylidene)hydantoin.

E. 1 - (6 - Carboxyhexyl) - 5 - (3 - hydroxyoctyl)hydantoin

A solution of 1 - (6 - carboxyhexyl) - 5 - [(*E*) - 3 - oxo - octylidene]hydantoin (3.06 g) in EtOH (60 ml) was stirred with 10% palladised charcoal (200 mg) under hydrogen at room temperature and pressure, absorption of 1 molecular equivalent of hydrogen occurring in 2 hours. The catalyst was filtered, the filtrate was evaporated *in vacuo*, and the residual gum was set aside to give a mass of colourless crystals. The crystals were suspended in ether (4 ml) and collected, affording pure 1 - (6 - carboxyhexyl) - 5 - (3 - oxo - octyl)hydantoin, m.p. 84.5—86°. A stirred suspension of 0.5 g of this compound in water (15 ml) at 0°C was treated with $NaHCO_3$ (0.36 g) and then, during 3 minutes, with sodium borohydride (54 mg). After 45 min., more sodium borohydride (54 mg) was added and, after a further 1¼ hours, the clear solution was set aside at room temperature for 1¼ hours. The solution was then acidified to Congo Red with hydrochloric acid, the liberated carboxylic acid was extracted into chloroform, and the chloroform solution was washed with water and dried over magnesium sulphate. Evaporation of the solvent afforded 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxyoctyl)hydantoin as a mixture of diastereomers which was subjected to HPLC (SiO_2, $CHCl_3$/MeOH/HOAc 97.75:1.25:1.0), affording the individual diastereomers as colourless gums, Rf 0.44 and 0.40 (relative to 0.64 for a marker of the starting oxo-compound) on SiO_2 in $CHCl_3$/MeOH/HOAc 90:5:5.

Interconversion of the diastereomers

The diastereomer of m.p. 108—110° (3.1 g) was dissolved in *N*-sodium hydroxide solution (50 ml) and the solution was left at room temperature for 18 hours. The solution was acidified and extracted with ether. The ether solution was washed with water, dried and evaporated to give a colourless glass (3.1 g), shown by thin-layer chromatography to be a mixture of the starting material with the other diastereomer. Separation of the mixture by HPLC gave the diastereomers of m.p. 97—99° (1.34 g) and m.p. 108—110° (1.33 g), identical with those described above.

Example 38

Preparation of 5-(6-carboxyhex-2(Z)-enyl-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin

Treatment of diethyl 2 - ((3 - cyclohexyl - 3 - hydroxypropyl)amino)non - 2 - enedioate, prepared according to Example 38 of our co-pending UK application No. 9171/76 (Serial No. 1595693) with potassium cyanate and hydrochloric acid and hydrolysis of the resulting hydantoin ester as in Reference Example A gave 5 - (6 - carboxyhex - 2(Z) - enyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin as a yellow oil, tending to solidify. By use of HPLC this compound was separated into its diastereomers, one forming small colourless prisms, m.p. 97—99°, and the other forming colourless needles, m.p. 108—110°.

Examples 39—41

By a series of reactions similar to that referred to Example 38:

39a. diethyl 2 - ((3 - hydroxyoctyl)amino)non - *cis* - 4 - enedioate;

40a. diethyl 2 - ((3 - hydroxy - 4,4 - dimethyl - 5 - phenylpentyl)amino)non - *cis* - 4 - enedioate; and

41a. diethyl 2 - ((3 - hydroxy - 3 - (*cis* - 4 - methylcyclohexyl)propyl)amino)non - *cis* - 4 - enedioate;

which were converted to the corresponding hydantoins:

39b. 5 - (6 - carboxyhex - 2(*Z*) - enyl) - 1 - (3 - hydroxyoctyl)hydantoin, one of the diastereomers forming colourless needles, m.p. 66—68°, the other a colourless viscous oil;

40b. 5 - (6 - carboxyhex - 2(*Z*) - enyl) - 1 - (3 - hydroxy - 4,4 - dimethyl - 5 - phenylpentyl)hydantoin, diastereomers, m.p. 116—117° and 66—70°; and

41b. 5 - (6 - Carboxyhex - 2(*Z*) - enyl) - 1 - (3 - hydroxy - 3 - (*cis* - 4 - methylcyclohexyl)propyl)hydantoin, diastereomers, m.p. 87—89° and 63—65°.

Example 42

Preparation of 5-(6-ethoxycarbonylhexyl)-1-(3-cyclohexyl-3-hydroxypropyl)hydantoin

A solution of 5 - (6 - carboxyhexyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin (diastereomer of m.p. 96—98°) (Example 13c) (4 g) in ethanol (60 ml) and concentrated sulphuric acid (1.6 ml) was allowed to stand at room temperature for 18 hours. The alcohol was evaporated, water was added, and the precipitated oil was extracted with diethyl ether. The ether solution was washed with sodium bicarbonate solution and with water, dried ($MgSO_4$) and evaporated to give a single diastereomer of 5 - (6 - ethoxycarbonylhexyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin as a colourless oil, soon solidifying, and crystallising from cyclohexane in small colourless plates, m.p. 62—63°.

EXAMPLES 43 to 46

By a series of reactions corresponding to those referred to in Example 38.

43a. diethyl 2 - ((3 - hydroxy - 4 - (3 - trifluoromethylphenoxy)butyl)amino)nonanedioate;

44a. diethyl 2 - ((3 - hydroxy - 5,5 - dimethylhexyl)amino)nonanedioate;

45a. diethyl 2 - ((3 - hydroxy - 3 - (*cis* - 4 - methylcyclohexyl)propylamino)nonanediote;

46a diethyl 2 - ((3 - hydroxy - 3 - (*trans* - 4 - methylcyclohexyl)propylamino)nonanedioate;

were converted to the corresponding hydantoins.

43b. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - (3 - trifluoromethylphenoxy)butyl)hydantoin, diastereomers, m.p. 118—120° and 105—107°

44b. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 5,5 - dimethylhexyl)hydantoin, diastereomers, m.p. 107—110° and 86—88°;

45b. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - (*cis* - 4 - methylcyclohexyl)propyl)hydantoin, diastereomers, m.p. 88—90° and 98—100°;

46b. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - (*trans* - 4 - methylcyclohexyl)propyl)hydantoin, diastereomers, m.p. 87—89° and 99—101°;

EXAMPLES 47—48

Similarly were prepared:

47. 5 - (6 - carboxyhexyl) - 1 - (3 - (3,3 - dimethylcyclobutyl) - 3 - hydroxypropyl)hydantoin;

48. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 5 - ethoxypentyl)hydantoin.

In the following examples the hydantoins are designated thus:

Compound 1: 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin

Compound 3: 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethylpentyl)hydantoin

Compound 5: 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxynonyl)hydantoin

Compound 8: 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyloctyl)hydantoin

Compound 10: 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclobutylpropyl)hydantoin

Compound 11: 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclopentylpropyl)hydantoin

Compound 13: 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin.

Where a particular diastereomer is used, this is indicated by reference to its melting point.

EXAMPLE A

Cardiovascular effects in rats

Male normotensive rats Wistar (Charles River) strain, (250—350 g) were anesthetised (chloroform) prior to cannulation of the left femoral vein and anesthesia maintained by intravenous chloralose (60 mg/kg). Pulsatile blood pressure was recorded from the left femoral artery with an electronic transducer (Bell and Howell Type 4-327 L221) and integrated heart rate was measured with a cardiotachometer triggered from the arterial pressure waves.

The test compound was administered as a solution in physiological saline by intravenous injection *via* the femoral cannula. The responses recorded were allowed to return to the preinjection levels between successive administrations.

Injections of the vehical alone in volumes equivalent to those containing drug did not produce hypotension.

Compound	Dose	Mean fall in blood pressure mmHg
PGE_2	4μg/kg	28
,,	16μg/kg	44
Compound 1	10μg/kg	14
,,	1mg/kg	42
Compound 5	3mg/kg	40
Compound 8	3mg/kg	22

EXAMPLE B

Inhibition of Platelet Aggregation

Aggregation of platelets in 1 ml. of fresh human platelet rich plasma (PRP) was monitored in a Born aggregometer.

The compound to be tested was added to the PRP at the desired concentration, and the resulting mixture incubated at 37°C for 1 minute after which platelet aggregation was stimulated by the addition of adenosine diphosphate (ADP) to a concentration of 5μM.

The anti-aggregatory effect of the compound was assessed by measuring the percentage inhibition of platelet aggregation in the presence of the compound as compared when it was completely absent.

Compound	Concentration	% Inhibition of Aggregation
PGE_1	15ng/ml	33
,,	20ng/ml	47
,,	30ng/ml	63
,,	40ng/ml	69
Compound 11 (m.p. 116—117°)	0.5ng/ml	25
,,	1.0ng/ml	51
,,	2.0ng/ml	79
,,	4.0ng/ml	94

Using comparisons such as this the following relative potencies were demonstrated with respect to PGE_1. Compound 2 (m.p. 76—78°), 12.5x; Compound 4 (m.p. 144—146°), 0.05x; Compound 11 (114—116°), 5.2x; Compound 12 (m.p. 116—117°), 12.5x; and Compound 14 (m.p. 96—98°), 16x.

EXAMPLE C

At an intravenous dose of 30μg/kg, Compound 1 completely inhibited pentagastrin-induced gastric acid secretion in rats.

EXAMPLE D

An intravenous injection of Compound 8 (50μg/kg) was found to completely antagonise histamine-induced broncho-constriction in anaesthetised guinea-pigs.

EXAMPLE E

Intravenous infusions of Compound 1 (m.p. 76—78°C) at a dose of 250 μg/min have been found to reduce electrically-induced arterial thrombosis in anaesthetised rabbits.

EXAMPLE F

Tablet	In one tablet
Compound 11 (m.p. 116—117°)	5.0 mg
Lactose B.P.	82.0 mg
Starch B.P.	10.0 mg
Povidone B.P.C.	2.0 mg
Magnesium Stearate	1.0 mg

Mix together the Compound 11, lactose and starch. Granulate the powders using a solution of the povidone in Purified Water. Dry the granules, add the Magnesium Stearate and compress to produce tablets, 100 mg per tablet.

EXAMPLE G

Capsule	In one capsule
Compound 11 (m.p. 116—117°)	10 mg
Lactose	79 mg
Starch	10 mg
Magnesium Stearate	1 mg

Mix the powders in a powder blender, fill into hard gelatin capsules, 100 mg per capsule.

EXAMPLE H

1 μg/ml Injection

Compound 11 (m.p. 116—117°)	100 μg
Water for Injection	to...100 ml

Dissolve the Compound 11 in the Water for Injection. Sterilise the solution by filtration through a membrane filter, 0.22 μm pore size, collecting the filtrate in a sterile receiver. Under aseptic conditions, fill the solution into sterile glass ampoules, 1 ml per ampoule. Seal by fusion of the glass.

EXAMPLE I

10 μg/ml Injection

Compound 11 (m.p. 116—117°)	1 mg
Ethyl Alcohol	10 ml
Propylene Glycol	30 ml
Water for Injection	to...100 ml

Dissolve the Compound 11 in the Ethyl Alcohol, add the Propylene glycol and dilute to volume with Water for Injection.

Sterilise the solution by filtration through a membrane filter, 0.22 μm pore size, collecting the filtrate in a sterile vessel. Under aseptic conditions, fill the solution into sterile glass vials, 10 ml per vial. Close with a sterile rubber plug and secure with an aluminium collar.

EXAMPLE J

100 μg Single dose injection (freeze-dried)

Compound 11 (m.p. 116—117°)	10.0 mg
Mannitol	2.5 g
N/10 Sodium Hydroxide Solution	qs to pH 10.0
Water for Injection	to...100.0 ml

Suspend the Compound 11 in approximately 20 ml Water. Add sufficient Sodium Hydroxide Solution to produce pH 10 and stir to dissolve the Compound 11. Add and dissolve the Mannitol and dilute to volume with Water for Injection.

Sterilise the solution by passage through a membrane filter, 0.22 μm pore size and distribute aseptically into sterile vials, 1 ml per vial. Freeze dry the solutions and seal the containers under aseptic conditions with rubber closures. Each vial contains 100 μg Compound 11 as its freeze-dried Sodium salt.

EXAMPLE K

Suppository

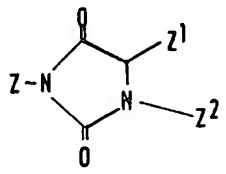
Compound 11 (m.p. 116—117°)	3 mg
Massa Esterinum C	to...2 mg

Melt the suppository base at around 40°C. Gradually incorporate the Compound 11 in fine powder and mix until homogeneous. Pour into suitable moulds and allow to set.

Massa Esterinum C is a commercially available suppository base consisting of a mixture of mono-, di- and tri-glycerides of saturated vegetable fatty acids. It is marketed by Henkel International, Dusseldorf.

WHAT WE CLAIM I:—

1. A compound of formula (I)



(I)

wherein Z is hydrogen;

one of Z^1 and Z^2 is represented by the group $—CH_2—X—X^1—X^2$

wherein X is phenylene, *cis* —CH=CH— or $—CH_2CH_2—$; X^1 is a covalent bond or a straight or branched alkylene chain having 1 to 6 carbon atoms optionally having one of its methylene groups replaced by oxa (—O—) provided that at least one carbon atom separates the oxa group from a —CH=CH— or —CO— group; and X^2 is selected from carboxyl and alkoxycarbonyl;

and the other of Z^1 and Z^2 is represented by the group $—Y—Y^1—Y^2—Y^3$

wherein Y is $—CH_2—CH_2—$; Y^1 is carbonyl, methylene, methylene substituted by hydroxy or methylene substituted by hydroxy and alkyl Y^2 is a covalent bond or straight or branched alkylene having 1 to 7 carbon atoms; Y^3 is hydrogen, hydroxy, alkoxy having 1 to 7 carbon atoms, benzyl, phenoxy or benzyloxy, wherein each of benzyl, phenozy and benzyloxy may be substituted in the benzene ring by one or more groups selected from hydroxy, halo, nitro, amino, acylamino, alkenyl, alkoxy, phenyl and alkyl which may itself be substituted by one or more halo groups; provided that, when Y^2 is a covalent bond then Y^3 is not hydroxy when Y^1 includes hydroxy; or Y^2 is a covalent bond and Y^3 is cycloalkyl having 4 to 7 carbon atoms as hereinbefore defined; or salt thereof.

2. A compound according to claim 1, wherein X^1 is a covalent bond or a straight or branched alkylene chain having 1 to 6 carbon atoms.

3. A compound according to any preceding claim, wherein X is *cis* —CH=CH— or $—CH_2—CH_2—$.

4. A compound according to any preceding claim, wherein Y^2 is alkylene having 1 to 7 carbon atoms optionally substituted on the carbon adjacent Y^1 by one or two alkyl groups.

5. A compound according to any preceding claim, wherein X is *cis* —CH=CH— or $—CH_2—CH_2—$, X^1 is a covalent bond or alkylene having 1 to 6 carbon atoms; X^2 is carboxy or alkoxycarbonyl;

Y is $—CH_2—CH_2—$; Y^1 is carbonyl, methylene, methylene substituted by hydroxy or methylene substituted by hydroxy and alkyl; Y^2 is alkylene optionally substituted on the carbon adjacent Y^1 by one or two alkyl groups; and Y^3 is hydrogen.

6. A compound according to any preceding claim, wherein Y^1 is carbonyl, methylene substituted by hydroxy or methylene substituted by hydroxy and methyl.

7. A compound according to any preceding claim, wherein X and X^1 together form n-pentamethylene.

8. A compound according to any preceding claim, wherein Z^1 is $—CH_2—X—X^1—X^2$ as therein defined.

9. A compound according to claim 1,

wherein at least one of X to X^2 and Y to Y^3 have one of the values ascribed to them below:

(a) X is —CH=CH—;

(b) X^1 is a covalent bond or hexamethylene;

(c) Y^1 is carbonyl;

(d) Y^2 is alkylene having 1 to 7 carbon atoms substituted on the carbon adjacent Y^1 by one or two alkyl groups;

(e) Y^3 is hydroxy, alkoxy having 1 to 7 carbon atoms, phenoxy, or benzyl,

phenoxy or benzyloxy substituted in the benzene ring by one or more groups selected from hydroxy, amino, acylamino, alkenyl, alkoxy, phenyl and alkyl which may itself be substituted by one or more halo groups other than trifluoromethyl;

(f) Y^2 is a covalent bond and Y^3 is cyclobutyl.

10. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxyoctyl)hydantoin.
11. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxypentyl)hydantoin.
12. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethylpentyl)hydantoin.
13. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - methylpentyl)hydantoin.
14. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxynonyl)hydantoin.
15. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - methyloctyl)hydantoin.
16. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxydecyl)hydantoin.
17. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyloctyl)hydantoin.
18. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - ethylhexyl)hydantoin.
19. 5 - (6 - carboxyhexyl) - 1 - (3 - cyclobutyl - 3 - hydroxypropyl)hydantoin.
20. 5 - (6 - carboxyhexyl) - 1 - (3 - cyclopentyl - 3 - hydroxypropyl)hydantoin.
21. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4,4 - dimethyl - 5 - *m* - trifluoromethylphenylpentyl)hydantoin.
22. 5 - (6 - carboxyhexyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin.
23. 5 - (6 - carboxyhexyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin.
24. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - phenylbutyl)hydantoin.
25. 5 - (3 - carboxypropyl) - 1 - (3 - hydroxyoctyl)hydantoin.
26. 5 - (8 - carboxyoctyl) - 1 - (3 - hydroxyoctyl)hydantoin
27. 5 - (3 - carboxymethoxybenzyl) - 1 - (3 - hydroxyoctyl)hydantoin.
28. 5 - (3 - carboxymethoxybenzyl) - 1 - (3 - hydroxy - 4,4 - dimethylpentyl)hydantoin.
29. 5 - (3 - (2 - carboxyethylbenzyl) - 1 - (3 - hydroxyoctyl)hydantoin.
30. 5 - (3 - (2 - carboxyethylbenzyl)) - 1 - (3 - cyclobutyl - 3 - hydroxypropyl)hydantoin.
31. 5 - (3 - (2 - carboxyethylbenzyl)) - 1 - (3 - cyclopentyl - 3 - hydroxypropyl)hydantoin.
32. 5 - (3 - (2 - carboxyethylbenzyl)) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin.
33. 5 - (4 - carboxymethoxybutyl) - 1 - (3 - hydroxyoctyl)hydantoin.
34. 5 - (4 - carboxymethoxybutyl) - 1 - (3 - cyclopentyl - 3 - hydroxypropyl)hydantoin.
35. 5 - (6 - ethoxycarbonylhexyl) - 1 - (3 - oxo - octyl)hydantoin.
36. 5 - (6 - carboxyhexyl) - 1 - (3 - oxo - octyl - hydantoin.
37. 5 - (6 - ethoxycarbonylhexyl) - 1 - (5 - phenylpentyl)hydantoin.
38. 5 - (6 - carboxyhexyl) - 1 - (5 - phenylpentyl)hydantoin
39. 5 - (6 - ethoxycarbonylhexyl) - 1 - octylhydantoin
40. 5 - (6 - carboxyhexyl) - 1 - octylhydantoin.
41. 5 - (6 - carboxyhexyl) - 1 - (4 - propoxybutyl)hydantoin.
42. 5 - (6 - carboxyhexyl) - 1 - (4 - phenoxybutyl)hydantoin.
43. 5 - (6 - carboxyhexyl) - 1 - (4 - *m* - trifluoromethyl-phenoxybutyl)hydantoin.
44. 5 - (6 - carboxyhexyl) - 1 - (3 - *m* - tolyloxypropyl)hydantoin.
45. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxypropyl)hydantoin.
46. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - methyloctyl)hydantoin.
47. 1 - (6 - ethoxycarbonylhexyl) - 5 - octylhydantoin.
48. 1 - (6 - carboxyhexyl) - 5 - octylhydantoin.
49. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 5 - ethoxypentyl)hydantoin.
50. 1 - (6 - carboxyhexyl) - 5 - (3 - oxo - octyl)hydantoin.
51. 1 - (6 - carboxyhexyl) - 5 - (3 - hydroxyoctyl)hydantoin.
52. 5 - (6 - carboxyhex - 2(Z) - enyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin.
53. 5 - (6 - ethoxycarbonylhex - 2(Z) - enyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin.
54. 5 - (6 - carboxyhex - 2(Z) - enyl) - 1 - (3 - hydroxyoctyl)hydantoin.
55. 5 - (6 - carboxyhex - 2(Z) - enyl) - 1 - (3 - hydroxy - 4,4 - dimethyl - 5 - phenylpentyl)hydantoin.

56. 5 - (6 - carboxyhex - 2(Z) - enyl) - 1 - (3 - hydroxy - 3 - (*cis* - 4 - methylcyclohexyl)propyl)hydantoin.

57. 5 - (6 - ethoxycarbonylhexyl) - 1 - (3 - cyclohexyl - 3 - hydroxypropyl)hydantoin.

58. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 4 - (3 - trifluoromethylphenoxy)butyl)hydantoin.

59. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 5,5 - dimethylhexyl)hydantoin.

60. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - (*cis* - 4 - methylcyclohexyl)propyl)hydantoin.

61. 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - (*trans* - 4 - methylcyclohexyl)propyl)hydantoin.

62. 5 - (6 - carboxyhexyl) - 1 - (3 - (3,3 - dimethylcyclobutyl) - 3 - hydroxypropyl)hydantoin.

63. A compound according to any preceding claim which is a mixture of the diastereomer having the higher melting point together with the diastereomer having the lower melting point.

64. A compound according to any of claims 1 to 62 which is the diastereomer having the higher melting point.

65. A compound according to any of claims 1 to 62 which is the diastereomer having the lower melting point.

66. A mixture of the diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin identified hereinbefore as having the lower melting point together with its diastereomer identified hereinbefore as having the higher melting point, or a salt thereof.

67. The diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin identified hereinbefore as having the lower melting point or its diastereomer identified hereinbefore as having the higher melting point, or a salt of either of them.

68. A salt or, where appropriate, an ester of a compound according to any one of claims 10 to 62.

69. The diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin identified hereinbefore as having the higher melting point.

70. The diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin identified hereinbefore as having the lower melting point.

71. A composition comprising a compound of formula (I) as defined in any of claims 1 to 70 in association with a pharmaceutically acceptable carrier.

72. A composition as claimed in claim 71 wherein the carrier is a liquid.

73. A composition as claimed in claim 71 or 72 in the form of a sterile injectable aqueous solution.

74. A composition as claimed in claim 72 or 73 comprising from 0.001 to 100 μg of a compound of formula (I) per millilitre.

75. A composition as claimed in claim 72, 73 or 74 in the form of a unit dose comprising from 0.01 to 1 mg of a compound of formula (I).

76. A composition as claimed in claim 71 wherein the carrier is a solid.

77. A composition as claimed in claim 76 in the form of a unit dose.

78. A composition as claimed in claim 76 or 77 in the form of a tablet, capsule, cachet or suppository.

79. A composition as claimed in claim 76, 77 or 78 comprising from 0.1 to 50 mg of a compound of formula (I).

80. A composition as claimed in any of claims 72 to 79 wherein the compound of formula (I) is 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin or a salt thereof.

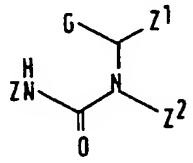
81. A composition comprising a mixture of the diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin identified hereinbefore as having the higher melting point together with its diastereomer identified hereinbefore as having the lower melting point, or a salt thereof, in association with a pharmaceutically acceptable carrier.

82. A composition comprising the diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin identified hereinbefore as having the higher melting point, or a salt thereof, in association with a pharmaceutically acceptable carrier.

83. A composition comprising the diastereomer of 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin identified hereinbefore as having

the lower melting point, or a salt thereof, in association with a pharmaceutically acceptable carrier.

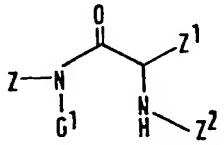
84. A method of preparing a compound of formula (I) as defined in any of claims 1 to 70 comprising cyclisation under acidic conditions or by heating of a compound of formula (II)



(II)

wherein G is carboxyl or a derivative thereof, and each of Z, Z^1 and Z^2 has the same meaning as in formula (I).

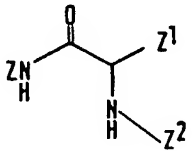
85. A method of preparing a compound of formula (I) as defined in any of claims 1 to 70 comprising cyclisation under acidic conditions or by heating of a compound of formula (VII)



(VII)

wherein G is carboxyl or a derivative thereof, and each of Z, Z^1 and Z^2 has the same meaning as in formula (I).

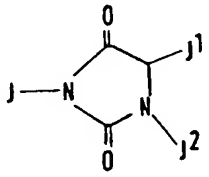
86. A method of preparing a compound of formula (I) as defined in any of claims 1 to 70 comprising reaction of a carbonic acid derivative with a compound of formula (IX)



(IX)

wherein each of Z, Z^1 and Z^2 has the same meaning as in formula (I).

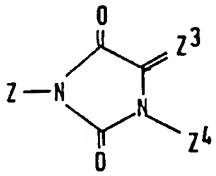
87. A method of preparing a compound of formula (I) as defined in any of claims 1 to 70 comprising alkylation of a compound of formula (X)



(X)

with a reactive ester derivative of an alcohol of formula $J^3.OH$, wherein J is hydrogen, J^1 is hydrogen or Z^1, J^2 is hydrogen or Z^2 and J^3 is Z^1 or Z^2 provided that one of J^1 and J^2 is hydrogen and J^3 does not have the same value as J^1 or J^2; in the definition of J^1, J^2 and J^3 each of Z^1 and Z^2 has the same meaning as in formula (I).

88. A method of preparing a compound of formula (I) as defined in any of claims 1 to 70 comprising reduction of a compound of formula (XI)



(XI)

wherein either Z^3 is $=CH—CH_2—Y^1—Y^2—Y^3$ and Z^4 is $—CH_2—X—X^1—X^2$ or Z^3 is $=CH—X—X^1—X^2$ and Z^4 is $—Y—Y^1—Y^2—Y^3$ in which each of X to X^2, Y to Y^3 and Z is as defined in formula (I).

89. A compound of formula (I) as defined in any of claims 1 to 71 when prepared by a process defined by any of claims 84 to 88.

90. 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin when prepared by a process defined by any of claims 84 to 88.

91. A method of inhibiting the aggregation of platelets which comprises the bringing of said platelets into association with an effective platelet aggregatory inhibiting amount of a compound of formula (I) as defined in any of claims 1 to 70.

92. A method for the treatment or prophylaxis of thrombosis in a mammal or mammalian tissue, excluding human, which comprises administration of a non-toxic, effective antithrombotic amount of a compound of formula (I) as defined in any of claims 1 to 70.

93. A method of lowering blood pressure in a mammal excluding man which comprises administration to the mammal of an effective hypotensive, non-toxic amount of a compound of formula (I) as defined in any of claims 1 to 70.

94. A method for inducing vasodilation in a mammal, excluding man, comprising administration to said mammal of a non-toxic effective vasodilatory amount of a compound of formula (I) as defined in any of claims 1 to 70.

95. A method for the treatment or prophylaxis of gastric lesions in a mammal excluding man comprising administration to said mammal of a non-toxic effective prophylactic or therapeutic amount of a compound of formula (I) as defined in any of claims 1 to 70.

96. A method for inducing bronchodilation in a mammal, excluding man, comprising administration to said mammal of a non-toxic, effective bronchodilatory amount of a compound of formula (I) as defined in any of claims 1 to 70.

97. A method for the treatment or prophylaxis of an allergic condition in a mammal, excluding man, comprising administration to said mammal of a non-toxic effective prophylactic or therapeutic amount of a compound of formula (I) as defined in any of claims 1 to 70.

98. A method of inducing abortion of a foetus in a mammal excluding human comprising administration to said mammal of a non-toxic effective abortifacient amount of a compound of formula (I) as defined in any of claims 1 to 70.

99. A method of inducing infertility in a mammal excluding human of a non-toxic effective contraceptive amount of a compound of formula (I) as defined in any of claims 1 to 70.

100. A method as claimed in any of claims 92 to 99 wherein the compound of formula (I) is administered at a daily dose of from 1 μg to 20 mg per kilogram of the mammal.

101. A method as claimed in any one of claims 92 to 99 which comprises an intraveneous infusion of the compound of formula (I).

102. A method as claimed in any of claims 91 to 101 wherein the compound of formula (I) is 5 - (6 - carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin.

103. The preparation of a compound of formula (I) as defined in claim 1 by a method substantially as hereinbefore described with particular reference to Examples 1 to 48.

104. 5 - (6 - Carboxyhexyl) - 1 - (3 - hydroxy - 3 - cyclohexylpropyl)hydantoin when prepared according to the process of Example 13.

105. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 in association with a pharmaceutically acceptable carrier substantially as hereinbefore described with particular reference to Examples G to L.

106. A method of preparing a composition as claimed in claim 48 which comprises admixture of the compound of formula (I) and a pharmaceutically acceptable carrier.

107. 5 - (6 - carboxyhex - 2(Z) - enyl) - 1 - (3 - hydroxyoctyl)hydantoin.

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